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Contrast Media Side Effects and Kounis Syndrome: Timeo Danaos et Dona Ferentes

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Kounis syndrome is defined as the occurrence of acute coronary events in the setting of allergic, hypersensitivity, or anaphylactic reactions. It is mediated by mast cell activation and the interaction of inflammatory cells, including T lymphocytes and macrophages. This process leads to the release of multiple inflammatory mediators, such as platelet-activating factor, histamine, neutral proteases (tryptase and chymase), arachidonic acid metabolites, cytokines, and chemokines. Kounis syndrome represents a unique form of acute vascular disorder that may involve not only the coronary arteries but also peripheral, cerebral, and mesenteric vessels as well as the venous system. Contrast media are widely used in diagnostic imaging to enhance visualization and characterization of pathological conditions. These agents can be administered via several routes, including oral, intravenous, intra-arterial, or rectal administration. Although most hypersensitivity reactions to contrast media are mild to moderate, severe complications such as anaphylaxis, cardiac arrest, and Kounis syndrome may occur. In particular, contrast media-induced Kounis syndrome has been associated with significant clinical consequences, including an increased risk of life-threatening cardiac events.

This narrative review aims to summarize current evidence regarding contrast media-related adverse effects, with a focus on hypersensitivity reactions, Kounis syndrome, and associated cardiovascular complications. Emphasis is also placed on preventive strategies, including the importance of obtaining a detailed patient history of prior hypersensitivity reactions prior to contrast administration, to reduce the risk of recurrence and severe outcomes.

INTRODUCTION

Contrast media are widely used in modern medical imaging to enhance differentiation between normal and pathological tissues, thereby improving diagnostic accuracy. These agents are administered prior to or during imaging procedures and play a critical role in modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound.[1] By altering the radiographic or magnetic properties of specific tissues, contrast agents facilitate visualization of anatomical structures and pathological processes that would otherwise be difficult to detect. Depending on the imaging modality, different types of contrast media are used, including iodinated agents and barium sulfate for X-ray and CT imaging, gadolinium-based agents for MRI, and microbubble or gas-based agents for ultrasound applications.[2] Contrast media can be administered via various routes, including oral, intravenous, intra-arterial, and rectal administration, depending on the clinical indication and the target anatomical region. While generally considered safe, their use is associated with a spectrum of adverse reactions, ranging from mild hypersensitivity responses to severe and potentially life-threatening complications. Among these, cardiovascular manifestations such as hypersensitivity-related cardiac dysfunction and Kounis syndrome have received increasing attention. Kounis syndrome represents a complex interaction between allergic reactions and acute coronary events, posing significant diagnostic and therapeutic challenges.

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This narrative review summarizes current evidence on cardiovascular hypersensitivity reactions, cardiac dysfunction, and Kounis syndrome associated with contrast media administration, with emphasis on their pathophysiology, clinical implications, and preventive strategies.

MATERIALS AND METHODS

We conducted a literature search on the PubMed, MEDLINE, Embase databases, and Google Scholar and updated it on 28 December 2025 with the keywords "contrast media," "contrast agents," "contrast chemicals," "contrast compounds," "contrast drugs," "contrast-enhanced," "contrast dye," "contrast reactions," "contrast materials," "allergy," "anaphylaxis," and "Kounis syndrome." Moreover, we searched the "brand iodine names": Xenetix, Bonorex/Omnipaque, Iomeron, Iopamiro, Ultravist, Optiray, Lugol's, Xymodine, Ioversol, Iopromide, Iopamidol, Iomeprol, Iobitridol, iodixanol, iodine tincture, iodine mild, iodine tincture decolorized, diatrizoate, strong iodine, and Ultravist; the "brand gadolinium names": Gadavist (gadobutrol), Dotarem (gadoterate meglumine), ProHance (gadoteridol), MultiHance (gadobenate dimeglumine), Eovist/Primovist (gadoxetate disodium), and Elucirem/Vueway (gadopiclenol); the "brand barium sulfate names": Entero Vu, E-Z-HD, NeuLumEx, Readi-Cat 2, Varibar Honey, Varibar Nectar, Varibar Pudding, Varibar Thin Honey, Varibar Thin Liquid, VoLumen, and Tagitol V; and the "brand microbubbles names": Definity, SonoVue, Optison, Lumasol, Luminity, perflutren, YJ Nozzle, New Spinor, and Eco-Bubble. To investigate the relationship between contrast media side effects and Kounis syndrome, a narrative review was carried out. To find pertinent publications published up to the end of January 2026, a literature search was conducted using the PubMed, Scopus, and Web of Science databases. Initially, 150 records were found. Fifty articles were eliminated for lack of relevance after titles and abstracts were screened. The eligibility of the remaining 100 articles was evaluated in full text. Fifteen of these were eliminated because they lacked clinical evidence or were not directly related to the subject. Although a rigorous systematic review technique was not strictly adhered to because this is a narrative review, attempts were made to guarantee a thorough and organized literature selection process.

CONTRAST MEDIA SUBSTANCES

There are several types of contrast media imaging, each appropriate for specific imaging techniques and diagnostic needs:

Iodine-based contrast is primarily used for X-ray and CT scans. Administered intravenously, orally, or rectally, this contrast can highlight blood vessels, kidneys, urinary tract, and the gastrointestinal tract.

Gadolinium-based contrast is employed in MRI. It is a rare-earth metal and is utilized in MRI contrast agents. Administered intravenously, it enhances the visibility of blood vessels, tumors, inflammation, and other lesions in various organs and soft tissues.

Barium sulfate contrast media are used for X-ray imaging of the gastrointestinal tract (esophagus, stomach, intestines). It is typically ingested or administered rectally.

Microbubble contrast media is used. Administered intravenously, these tiny gas bubbles enhance the visualization of blood flow in organs like the heart, liver, and kidneys.

Nanoparticles extend circulation duration, enhance bioavailability at tumor sites, and shield imaging agents from immune clearance. As contrast agents in modalities such as CT, optical imaging, MRI, and ultrasound, nanoparticles are revolutionizing biomedical imaging. They extend circulation duration, enhance bioavailability at tumor sites, and shield imaging agents from immune clearance. This leads to increased imaging sensitivity.

The contrast media categorized as ionic, non-ionic, and iodine-based agents are classified as low-osmolar and non-ionic based on their properties, such as osmolarity. The most frequently used agents are gadolinium for MRI, iodine-based contrast for CT/X-ray, and barium for gastrointestinal tract imaging. Negative agents, such as air, can also be utilized for X-ray/CT. Contrast media include substances such as iodine solutions or barium sulfate suspensions that are relatively opaque to X-rays and are injected or swallowed into the body to contrast an internal part such as the kidneys, blood vessels, or gastrointestinal tract with its surrounding tissue in radiographic visualization.[3] In medical imaging, contrast media are used to enhance the contrast of bodily fluids or structures. Unlike radiopharmaceuticals, which release radiation, contrast media absorb or modify environmental electromagnetic or ultrasound signals. Contrast compounds in X-ray imaging increase a target tissue or structure's radiodensity. Contrast drugs reduce, or sometimes lengthen, the relaxation periods of nuclei within bodily tissues in MRI to change the contrast in the picture.[4]

Since iodine is the radiopaque component of all iodinated contrast agents, the concentration of iodine in these agents determines the radiopacity resulting from their administration. The most common method of administering iodinated contrast agents is intravascular injection; however, due to the capillary permeability of contrast molecules, the material rapidly shifts to the extravascular area.[5]

Iodinated substances are occasionally used as rectal or oral contrast agents to improve imaging of the bowel and stomach. Nonetheless, the most common contrast agent used for gastrointestinal imaging is barium sulfate. The patient either receives this solution as an enema into the rectum or consumes it orally.

Certain forms of contrast media have been proven to be effective for various imaging methods. Each contrast media procedure operates at the suspected condition's natural site. For example, oral contrast media examinations may focus on the stomach or oesophagus, while rectal contrast media examinations highlight the colon or small intestine.[6] The contrast media are employed in the following manner, locations, and techniques:

Oral contrast media: Barium sulfate-containing contrast agents can be administered orally by swallowing for gastrointestinal tract CT, fluoroscopy, and X-ray imaging. Barium sulfate is sometimes replaced by iodine-based contrast media. The most common method of administering oral contrast agents is still barium sulfate, which comes in a variety of forms, including powder, liquid, paste, and pills.[7] The pharynx, oesophagus, stomach, small intestine, and large intestine (colon) are among the areas where oral contrast agents are used.

Intravenous contrast media: For intravenous injections used in CT, fluoroscopic, and X-ray imaging, contrast media are iodine-based. Gadolinium injections are used by radiologists for MRI. By altering the magnetic properties of water molecules, gadolinium increases the rate at which protons realign with the magnetic field. Thus, the image appears brighter when the proton moves more quickly. For CT scans, intravenous contrast is the most commonly used agent. In some situations, speed is necessary for the bolus to remain compact.[8] Intravenous contrast media injections are intended to highlight the following bodily parts: internal organs (brain, breasts, heart, lungs, liver, adrenal glands, kidneys, gallbladder, pancreas, uterus, and spleen), gastrointestinal system (small intestine, large intestine, and stomach), arteries and veins (brain vessels, neck, chest, abdomen, pelvis, and legs), and soft tissues (skin, muscle, and fat).

Rectal contrast media: For rectal contrast media, barium sulfate is used in an enema. To highlight the lower gastrointestinal tract and differentiate the colon and rectum regions of the body, this contrast media technique is used in X-ray, fluoroscopy, and CT scans. In some situations, iodine-based contrast agents may be used for the same purpose. Since the majority of the water-soluble contrast agents used in this procedure contain barium, rectal contrast media solutions are frequently referred to as barium enemas.[9]

SIDE EFFECTS OF CONTRAST MEDIA

Contrast media-related adverse responses can range from mild, such as nausea, a metallic taste, or skin redness, to serious, including severe allergic reactions, renal damage, or cardiac problems; these reactions typically occur during the first sixty minutes following treatment. Although these agents are often benign, there are risks associated with their use, such as thyroid disorders, contrast-induced kidney problems, and nephrogenic systemic fibrosis (NSF) from gadolinium-based drugs, as presented in Table 1. Skin rashes may develop considerably later, even up to 7 days following the treatment.[10]

a) Iodine-containing contrast can trigger adverse reactions in individuals, presenting a spectrum from mild to severe. Many people may experience mild skin irritation a few hours after the contrast agent is administered. If a patient encounters severe symptoms, seeking medical advice is crucial, as intervention may be needed. In the realm of mild reactions, symptoms may include nausea, headache, itching, skin redness, and mild skin eruptions. More severe side effects may include major skin eruptions, bronchospasm, irregular heart rate, hypertension or hypotension, or even breathlessness. Contrast agents can lead to dangerous reactions, manifesting as labored breathing, severe hypotension, bronchospasm, seizures, and Kounis syndrome.[11]

b) Gadolinium-based contrast adverse events are rather uncommon, occurring in 0.04-0.3% of administrations, of which 0.4-9% are severe. Injection-site discomfort, headache, nausea, and dizziness can occur in less than 2.5% of instances. Both acute and persistent adverse effects are possible. Patients who have previously experienced a hypersensitivity episode to gadolinium contrast agents have a 30% chance of experiencing another hypersensitivity episode. Gadolinium may cause NSF in some patients with kidney disease who undergo MRI. NSF is characterized by thickening and scarring of connective tissue. Although this is a rare complication, patients with severe kidney disease should avoid gadolinium-based contrast agents. Additionally, Kounis syndrome can be induced.[12]

c) Barium sulfate contrast can induce stomach discomfort, loose stools, nausea, vomiting, and difficulty passing stools. Should these manifestations intensify or persist, or if itching, skin redness, throat swelling, dyspnea, difficulty swallowing, hoarseness, restlessness, disorientation, elevated heart rate, or unusually light-colored skin develop, prompt medical attention is necessary. Individuals who have previously experienced conditions such as asthma, allergic reactions, cystic fibrosis, significant fluid loss due to constipation or other causes, bowel obstruction, or bowel rupture may also have adverse reactions. These individuals face an increased likelihood of experiencing unfavorable effects.[13]

d) Microbubble contrast agents are typically safe for use, although they can uncommonly result in adverse reactions ranging from minor issues such as headache, nausea, and lightheadedness to critical cardiac and pulmonary events. The majority of these reactions resolve spontaneously, but in extreme instances, individuals might experience anaphylactic shock, chest discomfort, arrhythmias, or Kounis syndrome.[14,15] In case of any adverse effects during treatment, it appears that the entire body's regions and structures are under the influence of the contrast agents being utilized. Tiny gas bubbles are injected into microbubble contrast media and are stabilized by a supporting shell. After injection of the microbubble contrast agent into the bloodstream, ultrasonography equipment is used to differentiate between the surrounding tissue and the gas bubbles. As a result, the procedure produces a clearly contrasted ultrasound image. Both targeted and untargeted microbubble contrast agents are available. The bubbles in targeted microbubble contrast agents adhere to a particular part of the body where molecules are bound to the gas surface.[16]

Nanoparticle agents have the potential to be novel agents for therapeutic and targeted imaging applications, which are currently the focus of extensive research. These include gold nanoparticles and superparamagnetic iron oxide nanoparticles that are designed to enhance MRI clarity, safety, and targeted distribution.[17] While nanoparticles provide X-ray attenuation and the possibility of targeted molecular imaging, superparamagnetic iron oxide nanoparticles work by causing T2 relaxation shortening for image contrast, providing an alternative or complementary method. Compared with conventional contrast agents, these agents offer superior safety, specificity, and multifunctionality.[18] Although anaphylaxis and Kounis syndrome have not been linked to nanoparticles used as contrast material, lipid nanoparticle-based coronavirus disease 2019 (COVID-19) vaccines and severe acute respiratory syndrome coronavirus 2 lipid-nanoparticle-based mRNA vaccination have been associated with allergic reactions and anaphylaxis.[19] It has been shown that there is an etiopathogenetic relationship between Kounis syndrome type I and COVID-19, associated with cytokine storm.[20]

TABLE 1. Iodine, Gadolinium, Barium Sulfate, Microbubble, and Nanoparticle Side Effects.

Iodine	1. Headaches, bloating, stomach pain, nausea, vomiting, and diarrhea. 2. Renal impairment, including anuria or reduced urine output after the use of contrast agents. 3. Skin eruptions, arrhythmias, dyspnea, and bronchospasm. 4. Hypersensitivity reactions, including skin rashes and itching, to severe reactions such as potentially fatal anaphylactic shock, Kounis syndrome, and rarely hyperthyroidism.
Gadolinium	1. Future gadolinium reactions are eight times more likely after a prior reaction. 2. Digestive: nausea, vomiting, and abdominal pain. 3. Neurological: paresthesia, headache, and vertigo. 4. Injection site reactions: discomfort, pain, warmth, or coldness. 5. Skin reactions: itching, rash, and urticaria. 6. Sensory/Other: fatigue, throat discomfort, and metallic taste. **Uncommon and serious adverse events** 1. NSF: An uncommon and serious disorder that mainly affects patients with severe kidney disease, causing skin thickening and joint contractures. The risk of NSF is significantly increased by impaired renal function. 2. Severe allergic reactions: About 1 in 5,000 people experience symptoms similar to anaphylaxis, such as bronchospasm, laryngospasm, or facial edema. Individuals with allergies or asthma are more vulnerable to acute hypersensitivity reactions and Kounis syndrome. 3. Gadolinium retention/toxicity: long-term deposition in the brain and bones, with unknown clinical consequences and unclear clinical implications.
Microbubbles	1. Common reactions are mild and include flushing, injection site reactions, headache, dizziness, and numbness. 2. Anaphylactic shock, back pain, chest pain, nausea and vomiting, skin allergy, and Kounis syndrome.
Barium sulfates	1. Confusion, coughing or hematemesis, dizziness, hives or welts, itching, skin rash, chest tightness, tachyarrhythmias, bradyarrhythmias, and Kounis syndrome. 2. Aspiration pneumonitis, barium impaction, melena, granuloma formation, hematuria, intravasation, embolization, and peritonitis following intestinal perforation, vasovagal and syncopal episodes. 3. Bloating, constipation, cramping, stomach pain, dyspnea, noisy breathing, and syncope. 4. Anxiety, blurred vision, bruising, cough, postural hypotension, persistent bleeding or oozing from puncture sites (mouth or nose), skin reactions, sweating, and unusual tiredness or weakness.
Nanoparticles	1. Decreased cytoskeletal disruption, decreased macrophage mobility, decreased phagocytosis, and decreased macrophage function. 2. Pro-inflammatory activity increase and the production of mediators such as cytokines 3. Negative impacts on vascular homeostasis and cardiac functioning.

NSF, nephrogenic systemic fibrosis.

CONTRAST MEDIA ANAPHYLAXIS AND KOUNIS SYNDROME

Cardiovascular symptoms associated with anaphylaxis, anaphylactoid reactions, allergy, or hypersensitivity reactions were initially categorized as acute carditis, morphologic cardiac reactions, or rheumatic carditis of unknown origin.[21] A unique type of acute vascular disease, Kounis syndrome, impacts the venous, cerebral, mesenteric, peripheral, and coronary systems.[21] Currently, Kounis syndrome is used to characterize coronary symptoms associated with conditions involving mast cell activation and interactions between inflammatory cells, such as T-lymphocytes and macrophages, which further cause allergic, hypersensitivity, anaphylactic reactions, or anaphylactic shock Figure 1. Among the inflammatory mediators that induce Kounis syndrome are platelet-activating factor, histamine, neutral proteases such as tryptase and chymase, products of arachidonic acid, and a variety of cytokines and chemokines released during the activation process.[21,22] Moreover, acute allergic reactions caused by contrast media, which act as a rapid and intense physical stressor, might cause Takotsubo syndrome.[23,24]

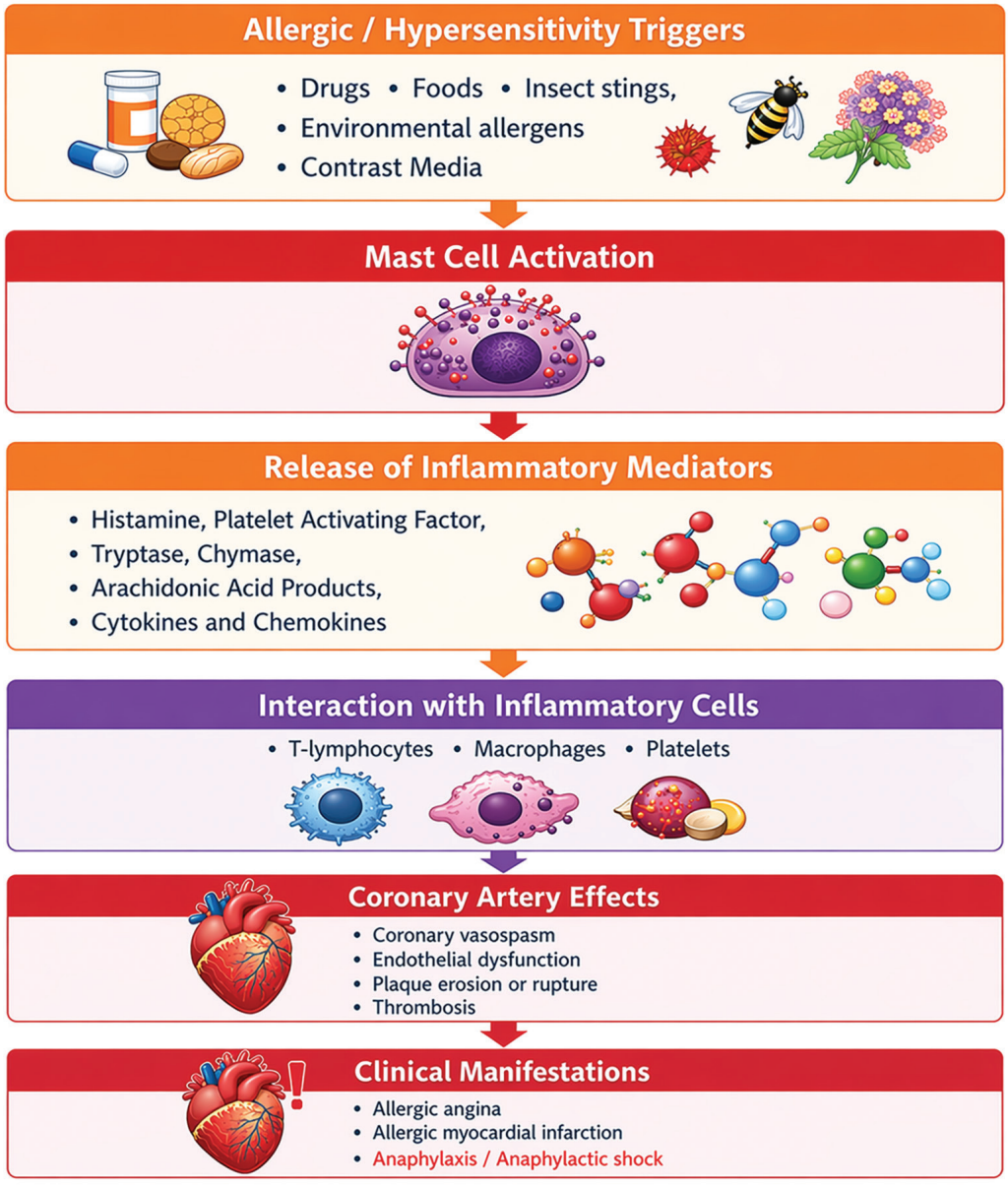

FIG. 1. The pathophysiological mechanism of Kounis syndrome with a summary of causes including contrast media, mast cell activation, inflammatory mediators, coronary artery effects and clinical manifestations.

Recent research[25] indicates that the prevalence of Kounis syndrome in those who have experienced an allergic, hypersensitive, anaphylactic, or anaphylactoid insult ranges from 1.1% to 3.4%. The National Inpatient Sample was used from 2007 to 2014 to evaluate baseline demographics and comorbidities with Kounis syndrome among patients mostly admitted for anaphylactic, hypersensitive, or allergic reactions.[26]

TABLE 2. Basic Details on Patients with Kounis Syndrome Caused by Iodines.

Country	First author	Sex/age	Trigger substance	Ref. No.	Administration
Japan	Tomida et al.	Male, 74 y	Iopamidol	**27**	Intravenous (type III KS)
Greece	Kogias et al.	Male, 48 y	Ultravist	**28**	Intravenous (during excretory urography)
Switzerland	Zmolik et al.	Female, 60 y	Ultravist	**29**	Intravenous (during CT scan → type I Kounis)
Japan	Kurokawa et al.	Male, 77 y	Iopamidol	**30**	Intravenous (during CT → cardiac arrest; subsequent CAG showed coronary spasm (type I Kounis), resolved with intracoronary nitrates)
France	Darwish et al.	Male, 57 y	Visipaque	**31**	Intra-arterial during coronary angioplasty → type II Kounis (anaphylactic shock + diffuse vasospasm)
Romania	Benchea et al.	Male, 68 y	Iodine	**32**	Intra-coronary (during angiography→asystole, coronary spasm)
South Korea	Seong et al.	Pediatric patients (≤ 18 y, n = 13,172)	Xenetix, Bonorex/ Omnipaque, Iomeron, Iopamiro, Ultravist, Optiray	**33**	Intravenous (during contrast-enhanced CT)
China	Sun and Zhang	Male, 59 y	Iodophorol	**34**	Intra-coronary (during coronary angiography → type II Kounis with cardiogenic shock)
Japan	Okuda et al.	Male, 60 y	Iopamidol	**35**	Intravenous during contrast-enhanced CT → type III Kounis (stent thrombosis)
USA	Nasrollahi et al.	Male, 63 y	Iodine	**36**	Intravenous (during contrast-enhanced CT → type II Kounis)
USA	Singh et al.	Male, 54 y	Omnipaque	**37**	Intravenous [during contrast-enhanced CT → type II Kounis (NSTEMI)]
Japan	Nagasawa et al.	Female, 73 y	Iopamidol	**38**	Intravenous (during contrast-enhanced CT → possible Kounis syndrome with anaphylactic shock)
China	Wang et al.	Male, 50 y	Ioversol	**39**	Intra-coronary (during coronary angiography → type II Kounis with cardiogenic shock)
Malaysia	Wong and Ahmad Hatib	Male, 56 y	Ultravist®	**40**	Intravenous (during CT coronary angiography → type II Kounis with ST-elevation and shock)
Switzerland	Bonnet et al.	Male, 46 y	Iodine	**41**	Intra-coronary [during PCI → type III Kounis (acute stent thrombosis + coronary spasm)]

TABLE 2. Continued.

Country	First author	Sex/age	Trigger substance	Ref. No.	Administration
		7 males/1 female	Iodinated Contrast Media (8)	**42**	5 IV / 3 intraarterial
		Male, 48 y	Ultravist		Intravenous
		Male, 79 y	Visipaque		Intraarterial
		Male, 62 y	Iohexol		Intravenous
Multinational (Asia/Europe/USA/ Chile/Australia)	Wang et al.	Male, 71 y	Iodine or dextran-40		Intraarterial
		Male, 74 y	Iomeron		Intravenous
		Male, 59 y	Visipaque		Intraarterial
		Male, 78 y	Iohexol		Intravenous
		Female, 72 y	Iopromide gadoterate		Intravenous
China	Wang and Zhang	Male, 63 y	Iopromide	**43**	Intravenous (during coronary CT angiography → Kounis syndrome following anaphylactic shock)
USA	Prisco et al.	Female, 53 y	Iodine	**44**	Intra-coronary (during coronary angiography (FFR) → type I Kounis with cardiac arrest)
USA	Shahab and Sangha	Male, 66 y	Omnipaque	**45**	Intravenous (during contrast-enhanced imaging → type II Kounis syndrome)
Poland	Dorniak et al.	Female, 59 y	Iodine	**46**	Intravenous (during coronary CT angiography → type I Kounis (vasospasm with severe LVOT obstruction)
Tain	Chien et al.	Female, 81 y	Iodine	**47**	Intravenous (during contrast-enhanced CT → type I Kounis syndrome)
Japan	Shibuya et al.	Male, 60 y	Iopamiron	**48**	Intravenous [during contrast-enhanced CT → type III Kounis (stent thrombosis)]
Australia	Bhaskaran et al.	Male, 83 y	Omnipaque	**49**	Intra-coronary (during coronary angiography → type II Kounis)
China	Zhang et al.	Female, 77 y	Iodixanol	**50**	Intra-arterial during coronary angiography → type II Kounis syndrome
China	Xu et al.	Male, 38 y	Visipaque	**51**	Intravenous (during CT → delayed type I Kounis syndrome)

y, years old; IV, intravenous; CT, computed tomography; CAG, coronary angiography; KS, Kounis syndrome; STEMI, ST- elevation myocardial infarction; PCI, percutaneous coronary intervention; DES, drug eluting stent; MRI, magnetic resonance imaging; NSTEMI, non-ST-elevation myocardial infarction; CM, contrast media; GBCAs, Gadolinium-based contrast agents; SF, sulfur hexafluoride; FFR, fractional flow reserve; LVOT, left ventricular outflow tract; OCT, optical coherence tomography.

TABLE 3. Basic Details on Patients with Kounis Syndrome Caused by Gadolinium.

Country	First author	Sex/age	Trigger substance	Ref. No.	Administration
Croatia	Zlojtro et al.	Female, 46 y	Dotarem®	**52**	Intravenous (during brain MRI → type I Kounis syndrome)
Mexico	Macías et al.	Female, 57 y	Gadovist	**53**	Intravenous (during MRI → anaphylaxis leading to Kounis syndrome)
		Mixed cases: 4 cases (induced by Gadolinium)	Gadolinium-based contrast agent (4 cases) + 5 cases (unknown contrast media induced)	**42**	Intravenous (administration during imaging procedures)
China	Wang et al.	Male, 57 y	MultiHance		Intravenous
		Female, 46 y	Dotarem		Intravenous
		Male, 30 y	MultiHance		Intravenous
		Male, 45 y	Dotarem		Intravenous
USA	Abusnina et al.	Female, 53 y	Gadolinium	**54**	Intravenous (brain MRI → type I variant of Kounis syndrome)
Japan	Tanaka et al.	Male, 78 y	Magnevist	**55**	Intravenous (during MRI → ST-segment elevation)
USA	Amro et al.	Female, 52 y	MultiHance	**56**	Intravenous (during brain MRI → Kounis syndrome)
France	Demoulin et al.	(sex not specified), 81 y	Dotarem	**57**	Intravenous (during MRI → inferior MI + heart block, type II Kounis)

y, years old; IV, intravenous; MRI, magnetic resonance imaging; ST-segment, ST-segment (electrocardiographic finding); MI, myocardial infarction.

TABLE 4. Basic Details on Patients with Kounis Syndrome Caused by Microbubbles.

Country	First author	Sex/age	Trigger substance	Ref. No.	Administration
China	Wang et al.	Mixed cases; 1 case (induced by microbubbles)	Perflutren	42	Intravenous
		Male, 76 y			
USA	Levy et al.	Female, 39 y	Lumason	58	IV (during TTE→ anaphylaxis with cardiogenic shock)
USA	Corsi et al.	Male, 62 y	Perflutren	59	IV (during TTE → cardiac arrest)
USA	Yopes et al.	Male, 47 y	Lumason	60	IV (during TTE → Kounis syndrome type I/II)
Italy	Marchi et al.	Male, 44 y	SonoVue	61	IV [during stress perfusion echocardiography → type III Kounis (stent thrombosis)]
USA	Sagalov et al.	Male, 51 y	Lumason	62	IV (during TTE → ST-segment elevation/ type I Kounis Syndrome)
USA	Steinhauer et al.	Female, 49 y	Lumason	63	IV (during TTE → anaphylaxis + ACS)
The Netherlands	van Ginkel A. et al.	Male, 60 y	SonoVue	64	IV (bolus before dobutamine/echocardiographic contrast → allergic reaction + ST-segment elevation)
USA (multicenter)	Wei et al.	Large cohort study Male, 63 y	Perflutren	65	Retrospective analysis of 78,383 IV contrast administrations (used in TTE)
Spain	Portero-Portaz et al.	Female, 72 y	SonoVue	66	IV (during dobutamine stress echocardiography → type III Kounis syndrome/DES thrombosis)

y, years old; IV, intravenous; TTE, transthoracic echocardiography; ACS, acute coronary syndrome; DES, drug-eluting stent; Definity, perflutren lipid microsphere injectable suspension; Optison, perflutren protein-type A microspheres injectable suspension; Lumason, sulfur hexafluoride lipid-type A microspheres (known as SonoVue in Europe); SonoVue, Sulfur hexafluoride microbubble contrast agent.

The degranulation of mast cells and other interacting and related cells, including T-lymphocytes, macrophages, eosinophils, and platelets, produces a range of inflammatory mediators following an anaphylactic or allergic reaction or insult, which are the main causes of Kounis syndrome. In the Kounis syndrome cascade, acute ischemia, coronary spasm, atheromatous plaque erosion/rupture, and platelet activation can all be caused by derivatives of histamine, tryptase, and arachidonic acid as well as chymase, which is a converting enzyme. Kounis syndrome may be triggered[67] by medications, Hymenoptera stings, metals, foods, environmental exposures, diseases, and immunizations. Histamine, chymase, or arachidonic acid derivatives (leukotrienes, platelet-activating factor) can induce myocardial infarction type I, also known as ischemia with no obstructive coronary arteries, which affects 76.6% of patients with normal or near-normal coronary arteries. Type II Kounis syndrome, occurring in 22.3% of individuals with quiescent prior coronary disease, can also be brought on by acute myocardial infarction with platelet activation and similar conditions that cause type I. Because of stent polymers, stent metals, eluted medications, dual antiplatelet therapy, and environmental exposures, 5.1% of patients may exhibit type III stent thrombosis (subtype IIIa) or stent restenosis (subtype IIIb) Figure 2.

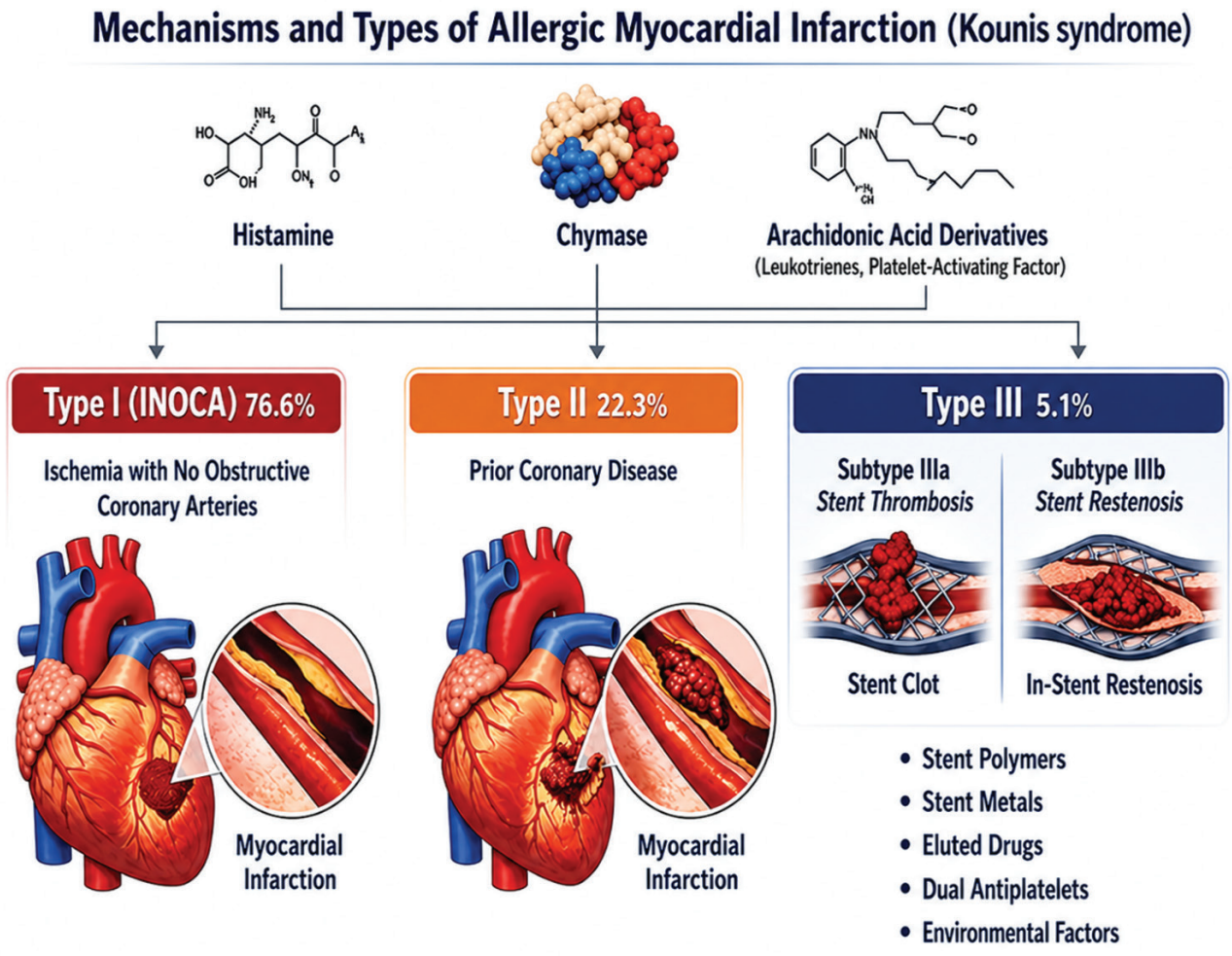

FIG. 2. The mechanism of type I, type II and type III of Kounis syndrome.
INOCA, ischemia with no obstructive coronary arteries.

DISCUSSION

Kounis syndrome is a cardiac hypersensitivity illness that has been reported across a wide age range, from two to eighty years. It encompasses a broad spectrum of mast cell activation disorders and has several, steadily increasing causes with expanding clinical manifestations. The cerebral and mesenteric arteries have been reported to be affected by Kounis-like syndromes, and the heart and entire arterial system are believed to be susceptible to allergic, hypersensitive, anaphylactic, and/or anaphylactoid events. Additionally, this syndrome may exacerbate mast cell activation disorders, and the affected areas appear to be the main locations and targets of hypersensitivity. Inflammatory mediators released either locally or in the systemic circulation after mast cell degranulation cause this condition. The activation of high- and low-affinity FcγRI, FcγRII, FcεRI, and FcεRII receptors on the platelet surface by mast cell mediators may also trigger the allergic thrombotic process. It has been shown that mast cells degranulate when relevant antigens bridge 2,000 adjacent antibodies that are attached to the cell surface to create the critical 1,000 bridges. Antibodies with distinct specificities can accomplish this process, and the severity of the disease, particularly in children, is correlated with the number of exposures within a specific time period.[68]

A recent study[69] discovered that contrast media-induced Kounis syndrome can result in major complications, such as a 7.7% mortality rate and a 23.1% cardiac arrest rate. Multiple organ failure and recurrent cardiac arrest still claimed the lives of two patients. When glucocorticoids and H1 (cetirizine and loratadine) and H2 (cimetidine and famotidine) receptor blockers are used to treat allergies, the symptoms of Kounis syndrome type I can be completely resolved in individuals.[70]

Corticosteroids and antihistamines should be used in conjunction with an acute coronary event protocol to initiate treatment for patients with type II Kounis syndrome.[70] They can inhibit the release of arachidonic acid from mast cell membranes by blocking phospholipase A2 and eicosanoid synthesis. Corticosteroids can also induce cell death and promote the synthesis of annexin or lipocortin, which are substances that regulate adhesion molecule expression, inflammatory cell activation, and transmigration and phagocytic processes. Drug exposure, antigen-antibody interactions, and hapten formation are some of the factors that have been implicated.

Systemic corticosteroids can trigger allergic responses through the following routes:[71]

a) Anaphylactic responses involving IgE antibodies to methylprednisolone have been documented.

b) Drugs that most frequently result in type 1 (immediate) adverse reactions include methylprednisolone and succinate esters of hydrocortisone.

c) Because succinate esters are more water-soluble and have a higher affinity for serum proteins, they facilitate hapten formation and act as complete antigens.

d) Methylprednisolone and hydrocortisone succinate esters are the drugs that most frequently result in type 1 (immediate) adverse reactions.

The current approach for acute myocardial infarction in patients with type III variants of Kounis syndrome includes prompt intrastent thrombus aspiration and histological analysis of the aspirated material. Moreover, nitrates and calcium channel blockers can prevent allergic coronary artery spasm. Beta-blockers should be avoided since they can exacerbate coronary artery spasm.

Life-saving drug in anaphylactic cases, can also trigger anaphylaxis on its own. A preservative present in all commercially available forms of adrenaline is sodium metabisulfite, according to Drug Facts and Comparisons, a standard pharmacy reference published by Wolters Kluwer and updated monthly. The food and pharmaceutical sectors frequently use sodium metabisulfite as an antioxidant. Metabisulfite, an additive in local anesthetics containing adrenaline, has been linked to cases of anaphylactic shock occurring during epidural anesthesia for caesarean sections. The occurrence of anaphylactic shock in sulfite-sensitive patients poses a therapeutic dilemma.

Fortunately, American Regent Inc., a pharmaceutical company located in New Albany, OH, USA, is now able to provide sulfite-free adrenaline to patients who are sensitive to it.[72] A possible alternative in this situation is glucagon, which has been successfully used to treat anaphylaxis in patients on β-blockers. International recommendations specifically suggest administering exogenous adrenaline intramuscularly at a dose of 0.01 mg/kg of a 1:1000 (1 mg/mL) solution11, with an adult maximum dose of 0.5 mg. This process is life-saving. On the other hand, dilute intravenous solutions [1:10,000 (0.1 mg/mL) or 1:100,000 (0.01 mg/mL)] may exacerbate coronary spasm.

Regarding contrast media, a recent study on gadolinium-based contrast agents-which are commonly used in MRI-raised concerns about their safety due to potential cytotoxic and genotoxic effects, especially at high doses or with repeated exposure. The cytogenotoxic potential of gadoteric acid in NIH3T3 fibroblast cells was assessed in this study using both *in vitro* and *in silico* methods. NIH3T3 cells were treated with increasing doses of gadoteric acid. The fibroblast cell line NIH/3T3 is derived from a mouse NIH/Swiss embryo. Studies on DNA transfection have found this cell line to be highly useful. Gadoteric acid generally showed dose-dependent cytotoxicity and moderate genotoxicity at high concentrations, indicating that DNA damage is caused by cytotoxic effects rather than a direct genotoxic mechanism.[73]

Examining the crucial but frequently overlooked issue of documenting hypersensitivity reactions to contrast media is important since incorrect documentation affects other medical specialties in addition to future imaging procedures. It is recommended to maintain accurate and up-to-date records of hypersensitivity episodes in order to ensure quality practice and improve patient outcomes.[74]

PERSPECTIVES

The European Society of Urogenital Radiology's Contrast Media Safety Committee revised its recommendations for preventing hypersensitivity reactions to intravascular, intravenous, or intra-arterial contrast media delivery.[75] To prevent a repeated hypersensitivity reaction and the resulting Kounis syndrome, it is crucial to determine whether the patient has ever had a reaction after

a contrast-enhanced test with confirmed hypersensitivity reaction symptoms. Determining the precise type of contrast material used is also crucial. Unfortunately, information about past hypersensitivity reactions is often missing or not well documented. In order to ensure that data regarding prior adverse reactions is appropriately collected, among other potential risk factors, a questionnaire should be used. Choosing the best preventive treatment to prevent additional reactions is one of the main issues in managing hypersensitivity reactions to contrast media. Premedication is no longer considered protective, and new research suggests using a different contrast agent.[76] The best course of action is to choose the safest contrast agent based on an evaluation of allergies and cardiology. Patients in urgent need of contrast media administration who have a history of severe hypersensitivity to an unknown contrast medium may avoid complicated scenarios by being referred promptly to allergologists and/or cardiologists. Given the complexity of these circumstances, a customized approach based on the patient's features, the indication for administering contrast media, and local preferences is advised.

CONCLUSION

Kounis syndrome caused by contrast media is not a common side effect. To ensure prompt diagnosis and appropriate treatment, cardiologists and radiologists should be aware of this rare but serious condition. To prevent a repeated hypersensitivity reaction and the resulting Kounis syndrome, physicians need to inquire about any past history of hypersensitivity or reaction after a contrast-enhanced test; a questionnaire should be used. A customized approach based on the patient's features, the indication for administering contrast media, and local preferences is advised. There are currently no universally accepted recommendations to help select an alternative contrast agent in these situations. This requirement is particularly important in cases of Kounis syndrome, where choosing an alternative contrast agent can be challenging.

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